Ind J Clin Biochem (Oct-Dec 2015) 30(4):424–429
DOI 10.1007/s12291-014-0465-x

ORIGINAL ARTICLE

The Acute Effects of Postprandial Hypertriglyceridemia on Coagulation Parameters in Normal and Overweight Individuals

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Received: 15 April 2014 / Accepted: 5 September 2014 / Published online: 10 October 2014

Abstract Postprandial hypertriglyceridemia may have a procoagulant effect and cause an activation of coagulation system. The measurement of postprandial triglyceride concentrations and coagulation parameters may give additional useful data besides the fasting measurement. Thus, we investigated the acute effects of hypertriglyceridemia after the meal in normal and overweight individuals. Fourteen overweight (Group I) and sixteen normal weight (Group II) voluntary participants were given fat-rich meal (700 kcal). Blood samples were obtained at fasting, 3rd and 6th hours. In both groups, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride (TG), fibrinogen, prothrombin time (PT), activated partial thromboplastin time, factor VII (FVII), factor IX (FIX), protein C and, protein S activities were measured. As might be expected, TG levels were higher in the postprandial state than the fasting state in both groups and also Group I subjects had higher levels rather than Group II at all states. One of our important finding finding was that PT levels were shorter in Group I at the fasting, postprandial 3rd and 6th hours than Group II ($P = 0.007$, $P = 0.033$, $P = 0.047$ respectively). Moreover, FVII and FIX activities were found as higher in Group I at the postprandial 3rd hour ($P = 0.047$, $P = 0.008$ respectively). In conclusion, the high activities of FVII and FIX and short PT levels may predispose to thrombosis in Group I, especially at postprandial states.

Keywords Postprandial · Hypertriglyceridemia · Coagulation · Overweight

Introduction

Plasma lipid levels are commonly higher in overweight individuals and these levels increase even more at the postprandial status. Postprandial lipid alterations may activate coagulation system and cause procoagulant effect. However, consequences of various diseases seem more aggressive in overweight individuals, and also mechanisms of these effects are not clear.

The main attention of the studies focusing on the role of lipids in hemostasis and probable mechanisms was on FVII which starts extrinsic coagulation pathway [1, 2]. High levels of postprandial plasma triglyceride (TG) may increase serum FVII activities and so, cause procoagulant effects [3, 4].

In vitro studies have shown that negative charge of free fatty acids on purified very low density lipoprotein cholesterol (VLDL), chylomicron and chylomicron remnants activates intrinsic coagulation pathway and FVII [5, 6].

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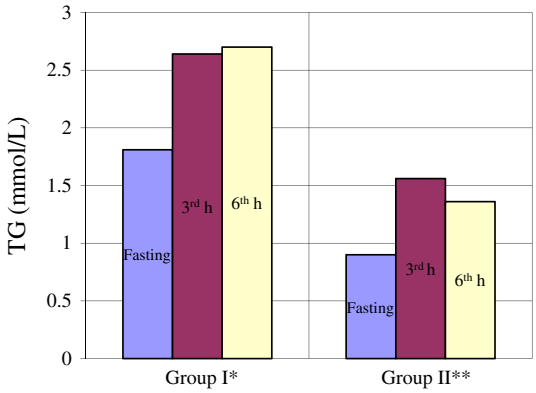

Fig. 1 The difference of triglyceride concentrations between fasting and postprandial states in Group I and Group II. *Group I* overweight individuals, *Group II* normal weight individuals, *TG* triglyceride. **P* value was <0.001 for fasting and postprandial 3rd hour and was 0.005 for fasting and postprandial 6th hour in Group I. ***P* value was 0.003 for fasting and postprandial 3rd hour and was 0.011 for fasting and postprandial 6th hour in Group II

Addition of fat to diet has been consistently shown to cause a rapid conversion of the FVII zymogen into its active form. Postprandial activation of FVII is dependent on lipolytic activity and this is mainly supported by large TG-rich lipoprotein of the VLDL class. Specific coagulation factor-deficient patients indicate that factor IX (FIX) is essential for the postprandial activation of FVII [7]. Indeed, TG-rich lipoproteins activate procallicrein postprandially, which might form an important initial event in FVII activation after consumption of high-fat meals [8]. There was strong positive correlation between FVII activity and plasma TG concentration, suggesting a probable interaction between FVII and TG-rich lipoprotein, but not with low density lipoprotein cholesterol (LDL) or high density lipoprotein cholesterol (HDL) in vivo [9, 10]. Moreover, lipemia activates FVII in individuals who had coronary vascular disease (CVD) and healthy subjects [11, 12].

FVII is structurally similar with FIX, prothrombin, protein C (PC) and protein S (PS). In hypertriglyceridemic subjects, not only FVII but also the other procoagulant vitamin K–dependent proteins are increased in plasma [13].

In this study, it was aimed to evaluate the acute effects of postprandial hypertriglyceridemia on coagulation system in both of normal and overweight individuals (Fig. 1).

Materials and Methods

Study Site and Subjects

This experimental study was carried out in the Ataturk Training and Research Hospital Clinical Biochemistry Laboratory in Izmir, Turkey. The study group consisted of thirty voluntary participants who were also the laboratory staff. Written informed consent was obtained from each participant before inclusion to the study. The procedures were in accordance with the guidelines of the Helsinki Declaration on human experimentation. Patient who were diagnosed diabetes mellitus, liver disease, thyroid dysfunction, renal disease and gastrointestinal tract disease, and receiving lipid-lowering therapy were excluded from the study.

The voluntary participants were divided into two groups according to their body mass index (BMI) and the subjects who had BMI over 25 were accepted as overweight. The study groups were as following:

Group I: BMI $>$ 25

Group II: BMI $=$ 20–25.

Subjects were instructed not to drink alcohol or to perform hard physical activities for 2 days before the test day. The descriptive characteristics of subjects were presented in Table 1.

Methods

After 12–14 h fasting, the baseline blood samples were drawn. Then, the participants ingested their test meals which were given between 8.00 and 9.00 a.m. Test meal included the total energy of 700 kcal and contained totally 59 % lipid, 27 % carbohydrate and, 14 % protein. Twenty-nine gram sunflower oil (260 kcal, composed of 37 % lipid), 75 g white fatty cheese (217 kcal, composed of 21 % lipid and 10 % protein) and 83 g wheat bread (223 kcal, composed of 1 % lipid and 27 % carbohydrate and 4 % protein) were the foods in their meals. The samples were subsequently drawn at 3rd and 6th hours from the participants. They only consumed the natural water, and rested in seated position throughout the study.

Blood was collected by using Vacuette® Standard tube holder and Vacuette® 21-gauge, 0.80 × 38 mm multisample needle (Vacuette, Greiner Bio-One, Kremsmünster, Austria).

1/9 trisodium citrated tubes were used to obtain plasma samples for hemostasis markers as prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen concentrations and PC, PS, FVII, FIX activities. These markers were measured with original reagents on the coagulation analyzer (ACL Futura Plus, Instrumentation Laboratory—IL, Milan, Italy) and the coefficient of variations (CV) were 3.6, 2.8,6.8, 4.7, 11.2, 1.9, 3.2 % respectively.

Vacutainer tubes without gel were used for the lipid determinations as TG, total cholesterol (T Chol) and, HDL cholesterol concentrations. They were measured on Olympus analyzer (Olympus AU2700 system reagent,

Table 1 The descriptive characteristics in Group I and Group II

Gender	Group I ($n = 14$)		Group II ($n = 16$)		P*
	7 male, 7 female		8 male, 8 female		
	Mean ± SD	Min–Max	Mean ± SD	Min–Max	
Age (years)	32.8 ± 3.0	27.0–38.0	31.3 ± 5.0	25.0–40.0	0.34
BMI (kg/m^2)	28.7 ± 1.7	26.1–32.7	22.2 ± 1.5	20.0–24.7	*0.01*

Group I overweight individuals, *Group II* normal weight individuals, *BMI* body mass index

* Statistically significant differences are in *Italics*

Table 2 *P* values of coagulation parameters and triglyseride in Group I and Group II at same time intervals

	Fasting			Postprandial 3rd hour			Postprandial 6th hour		
	Group I	Group II	P*	Group I	Group II	P*	Group I	Group II	P*
T Chol (mmol/L)	5.11 ± 0.73	4.52 ± 0.92	0.060	5.09 ± 0.73	4.48 ± 0.96	0.065	5.22 ± 0.71	4.61 ± 0.97	0.063
TG (mmol/L)	*1.81 ± 1.16*	*0.90 ± 0.33*	*0.006*	*2.64 ± 0.90*	*1.56 ± 0.49*	*<0.001*	*2.70 ± 1.14*	*1.36 ± 0.64*	*<0.001*
LDL (mmol/L)	3.16 ± 0.63	2.88 ± 0.83	0.319	2.79 ± 0.56	2.58 ± 0.90	0.465	2.89 ± 0.57	2.77 ± 0.91	0.681
HDL (mmol/L)	1.11 ± 0.26	1.21 ± 0.18	0.242	1.08 ± 0.25	1.18 ± 0.17	0.199	1.08 ± 0.28	1.21 ± 0.17	0.148
PT (s)	*11.8 ± 0.8*	*12.8 ± 1.0*	*0.007*	*12.0 ± 1.1*	*13.0 ± 1.4*	*0.033*	*12.0 ± 0.8*	*12.7 ± 1.0*	*0.047*
APTT (s)	30.5 ± 2.6	30.3 ± 2.7	0.907	30.4 ± 2.9	30.6 ± 2.3	0.803	29.9 ± 3.1	30.6 ± 2.2	0.468
Fbg (g/L)	3.47 ± 0.42	3.31 ± 0.70	0.468	3.29 ± 0.40	3.28 ± 0.70	0.986	3.58 ± 0.51	3.33 ± 0.73	0.304
F VII (%)	114.1 ± 23.7	95.8 ± 28.1	0.066	*112.2 ± 27.8*	*91.5 ± 28.4*	*0.047*	*114.7 ± 28.3*	*90.1 ± 25.8*	*0.021*
F IX (%)	*136.4 ± 23.7*	*107.9 ± 24.0*	*0.003*	*130.0 ± 19.5*	*108.1 ± 22.2*	*0.008*	121.4 ± 21.6	113.0 ± 21.7	0.295
PC (%)	112.1 ± 14.7	101.3 ± 21.5	0.126	111.3 ± 15.7	98.4 ± 21.3	0.074	114.6 ± 18.9	101.3 ± 21.6	0.085
PS (%)	100.1 ± 12.0	98.4 ± 11.7	0.697	96.6 ± 8.4	96.1 ± 13.0	0.901	100.3 ± 12.7	98.0 ± 12.0	0.616

Group I overweight individuals, *Group II* normal weight individuals, *T Chol* total cholesterol, *TG* triglyceride, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *Fbg* Fibrinogen, *FVII* factor VII, *FIX* factor IX, *PC* protein C, *PS* protein S

* Statistically significant differences are in *Italics*

Olympus Diagnostica GmbH, Lismeehan, O'Callaghan's Mills, Co. Clare, Ireland) and the CV were 1.76, 1.45, 1.92 %, respectively. The LDL cholesterol concentrations were calculated using the Friedewald formula. Internal and external quality control results for all tests were in acceptable limits during the study. All samples were separated by centrifugation at 1,500×*g* for 15 min and all parameters were measured within 30 min.

Statistical Analysis

Statistical package for Windows, Version 15.0, SPSS Inc. (Chicago, IL, USA) was used for statistical analysis. The distributions of the tests were determined using Kolmogorov–Smirnov test. Then, the parametric student t test was used for significant differences of normal distributed tests between groups. The significant differences were determined by Paired samples *t* test for each group. *P* values <0.05 were considered statistically significant.

Results

In this study, as might be expected, TG levels were higher in postprandial states than the baseline in both groups (Fig. 1). However, T Chol, HDL and LDL concentrations were not significantly changed among different time intervals of each groups ($P > 0.05$ for all). Moreover, we detected that Group I had higher levels of TG levels in comparison to Group II, but there were not any difference for other lipid parameters (Table 2).

One of our important finding was that PT levels were shorter in Group I than Group II at the fasting, postprandial 3rd and 6th hours. Beside this, there were not any changes at postprandial stages rather than baseline levels of PT and APTT levels for each groups.

Although statistical significant differences were not found for APTT and fibrinogen concentrations between groups at all stages, fibrinogen concentrations were shown moderately increase at postprandial 6th hour, conversely to

the decrease at postprandial 3rd hour than fasting state in Group I.

At postprandial stages, Group I have significantly higher levels of FVII and FIX activities than Group II and FVII activity was shown the decreasing trend towards postprandial 3rd and 6th hours in Group II, in paralel to prolongation of PT at postprandial 3rd hour than fasting and any changes of APTT.

One of the other findings as a procoagulant effect was about FIX activity which was shown the increasing trend towards both of postprandial states for Group II, in contrast to Group I decreasing levels comparison to baseline levels.

Although there were no statistical significant differences for PC and PS activities between groups, PS activities were shown the decreases for each groups at postprandial 3rd hour. In Group II, PC activities were significantly lower at postprandial 3rd hour, but not at postprandial 6th hour in comparison to baseline levels.

Discussion

The relationship between lipid profile and hemostasis was complex and not clear enough to understand. The present study showed the effects of postprandial hypertriglyceridemia on coagulation parameters for both of overweight and normal weight individuals. Although, APTT, fibrinogen concentrations, PC, PS activties in Group I were not significantly different from in Group II. There were some alterations in activities of FVII, FIX and PT as hemostasis parameters in both groups.

However, Group I have significantly higher levels of FVII activities than Group II, in which FVII activities did not show any changes at postprandial stage compared with fasting state. Contrarily, Bladbjerg et al. reported that FVII activity was increased after fat-rich meal at 4th and 6th hours [14]. A transient rise in FVII after a fat-rich meal has been shown previously [15, 16]. Conversely, Mortensen et al. reported a decline in the FVII concentration after meal in diabetic subjects [17]. In our study, the 59 % of energy from fat in the test meals may be too low to induce a lipemic response and then activate FVII levels. Sanders et al. did not detect any activation of FVII unless there was any fat intake in meal, increasing 70 % of energy [18]. However, an increase was observed in FVII until 6th hour postprandial time using 50.6 % of energy from fat in healthy young men [15]. Contrarily to our study, Silveira et al. concluded that both of healthy subjects and patients with manifested CVD had the increases for FVII activity within 3 h of oral fat tolerance test, consisting of 998 kcal in total energy content, which accounted for 60.2 % of energy from fat [19]. Those different findings may partly be explained by differences in study populations (i.e. young, healthy, or hyperlipemia). Our study population was consisted from homogeneous young individuals. Therefore the absence of any relation between postprandial serum TG concentration and FVII activity in young individuals do not exclude cumulative effect of hyperlipidemia on FVII activation in old individuals.

Overweight individuals have a risk of CVD and deep vein thrombosis, which can be explained by disturbances in the haemostatic and fibrinolytic systems. Indeed, obese subjects tend to have higher values of fibrinogen, FVII, Factor VIII (FVIII), von Willebrand factor and plasminogen activator inhibitor-1(PAI-1) compared to non-obese subjects. Weight loss seems to have a beneficial effect on FVII, probably mediated through a reduction in TG [20].

It was determined that FIX activity was higher in Group I compared to Group II, independently from postprandial state in our study. In parallel with our study, it was shown that obese individuals had higher activities of FIX, but not of fibrinogen [21]. Acquired obesity, independently from genetic factors, increases the activities of fibrinogen and FIX activity, beside the factors such as Factor XI (FXI), Factor XII (FXII), and PAI-1.

Fibrinogen levels and FIX activity were increased in the obese twins and strongly correlated with the measures of adiposity, inflammation, and insulin resistance among the twin individuals [22]. Several studies have shown that the obese individuals have higher plasma concentrations of all prothrombotic factors, as compared to non-obese controls, with a positive association with central fat. As to intervention strategies, dietary (i.e. low-fat high-fiber diet) and lifestyle (i.e. physical activity) measures have been demonstrated to be effective in improving the obesity-associated prothrombotic risk profile [23].

FIX activity which was shown in the increasing trend along the study for Group II, in contrast to Group I's decreasing levels at postprandial states comparison to baseline levels. A study that's similar to ours was from Xu et al. which concluded that individuals with hypertriglyceridemia had higher FIX activity but did not have any changes after fat- rich meal [24].

In our study, PT was shorter in Group I than in Group II ($P = 0.007$ at baseline) and didn't show any change at postprandial states ($P > 0.05$) in both groups. Increased BMI was shown that it was altering hemostasis and in parallel with PT [25] and APTT shortening [26]. However, Polac et al. showed that PT wasn't affected from fat-rich meal at postprandial state as similar to our study [27].

Xu et al. found that the vitamin K-dependent proteins (FVII, FIX, PT, PC and PS) associate with TG-rich lipoprotein in both fasting and in postprandial plasma, but not with LDL or HDL [24]. It was shown that the gradual increase of TG-rich lipoprotein, T Chol and HDL, decrease of LDL and little change of FVII and fibrinogen over 6 h

when the dairy butter fat modified to reduce the saturated: unsaturated fatty acid ratio and the conventional high saturated butter fat were given on two separate occasions to healthy men [28]. TG, HDL and FVII were important postprandial markers of CVD risk and the changes in fatty acid composition significantly affected only TG-rich lipoproteins among other postprandial markers of CVD risk, then it may be tried to modify through diet. In our study, high activity levels of FVII and FIX in Group I were associated with high TG concentrations and this association might show a possible interaction between the two.

There were many different results in studies which were mentioned about the acute effects of postprandial hypertriglyceridemia on coagulation parameters. However, the different analysis methods might affect the results [29] and also, plasma factor activities were affected from genetic and environmental factors [30, 31]. The fatty meal induces postprandial procoagulant tendency, the other reason of different results was the type of fat consumed by the participants. According to Delgado-Lista et al's study, the saturated fatty acid-rich dietary model has created more procoagulant environment than the model which was monounsaturated or carbohydrates plus n-3 fatty acids-rich [32]. Bladbjerg et al. observed similar effects of the monounsaturated fatty acids diet and the low-fat diet on the postprandial prothrombotic risk profile and coagulation activation in overweight subjects with more pronounced acute than long-term effects [33].

Many studies investigating the postprandial effects of lipids suffer the limitation that the fat load given is unrepresentative of the typical fat content of a meal, meaning that extrapolation of results to real-life situations may be not possible.

The limitations of our study were that the individuals were not grouped and evaluated according to their hypertriglyceridemia levels, the long-term nutritional habits and gender. Further studies are needed to enlighten the mechanism of fat-rich meals and the long-term effects of different fats on coagulation parameters to be helpful for new therapeutic approaches.

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